Applicants have amended the specification to correct trademark designations and typographical errors in a Preliminary Amendment filed October 30, 2000.

4. Priority Dates

The Examiner states that all pending claims enjoy the benefit under 35 U.S.C. §120 of USSN 08/539,142, filed 10/4/95. Applicants acknowledge and confirm priority to that parent application.

5. §102(e) Prior Art

Applicants acknowledge the present application will be examined under the pre-AIPA 35 U.S.C. §102(e) provisions.

6. §103(a) and Joint Inventorship of Claims

Applicants acknowledge the obligations under 37 CFR 1.56 and note that the pending claims are commonly owned by the joint inventors.

7. §102(e)

Claims 15, 16, 23-25, 29-32 and 36 stand rejected under 35 U.S.C. §102(e) as being anticipated by *Galy et al.* (USPN 6,015,554). Applicants respectfully traverse.

Galy et al. discloses compositions enriched for progenitor cells capable of differentiation into, *inter alia*, dendritic cells (DC), as well as methods of purifying or enriching for these progenitor cells (column 8). Methods of using enriched progenitor cell populations are discussed, such as using DC or DC precursors in a vaccine strategy whereby the cells are loaded with antigen and injected to induce a specific immune response (column 11, first paragraph). Example 8 describes an experiment to determine the differentiative potential of $CD34^+$ Lin^- $CD10^+$ and $CD34^+$ Lin^- $CD10^-$ cells by culturing the cells *in a cocktail containing 9 cytokines* (IL-1, IL-3, IL-6, IL-7, KL, GM-CSF, TNF, Flt3-L and EPO). This was done in order to support a broad spectrum of hematopoietic cells (columns 27 and 28).

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990). The identical invention must be shown in as complete detail as is contained in the . . . claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), *cert. denied*, 110 S.Ct. 154 (1989). The elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Galy et al. fails to satisfy the legal standard of anticipation under 35 U.S.C. §102(e) because it does not disclose the *identical* invention of the claims under consideration. As mentioned above, *Galy et al.* discloses culturing the hematopoietic progenitor cells *in a cocktail containing 9 cytokines* (IL-1, IL-3, IL-6, IL-7, KL, GM-CSF, TNF, Flt3-L and EPO) in order to support a broad spectrum of hematopoietic cells. This is not the method claimed by Applicants.

Applicants are claiming contacting hematopoietic stem or progenitor cells with Flt3-L *alone*, exposing the dendritic cells to an antigen and allowing the dendritic cells to process and express the antigen (claim 15, *et al.*) or in combination with GM-CSF (claim 16, *et al.*). *Galy et al.* does not disclose these elements and therefore does not anticipate Applicants' claimed invention. In addition, *Galy et al.* does not disclose the identical method of claim 29.

In sum, Applicants are claiming a method comprising of a series of steps arranged in a particular order. *Galy et al.* does not disclose the *identical steps arranged in the same order* as the claims at issue. Therefore, *Galy et al.* does not meet the legal requirements of an anticipating prior art reference. As such, Applicants respectfully request the rejection under §102(e) be properly withdrawn.

8. §103(a)

Claims 15, 16, 23-25, 29-32 and 36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Galy et al.* (USPN 6,015,554) in view of *Steinman et al.* (USPN 5,994,126).

Applicants respectfully traverse and submit that the disclosure of *Galy et al.* in view of *Steinman et al.* does render the present claims obvious under 35 U.S.C. §103(a) and that the combination of references does not meet the legal standard of *prima facie* obviousness.

Galy et al. discloses compositions enriched for progenitor cells capable of differentiation into, *inter alia*, dendritic cells (DC), as well as methods of purifying or enriching for these progenitor cells (column 8). Methods of using enriched progenitor cell populations are discussed, such as using DC or DC precursors in a vaccine strategy whereby the cells are loaded with antigen and injected to induce a specific immune response (column 11, first paragraph). Example 8 describes an experiment to determine the differentiative potential of $CD34^+$ Lin^- $CD10^+$ and $CD34^+$ Lin^- $CD10^-$ cells by culturing the cells *in a cocktail containing 9 cytokines* (IL-1, IL-3, IL-6, IL-7, KL, GM-CSF, TNF, Flt3-L and EPO). This was done "in order to support a broad spectrum of hematopoietic cells" (columns 27 and 28).

Steinman et al. teach methods of producing proliferating cultures of DC precursors and mature DC using GM-CSF and optionally other cytokines (see column 6, lines 37-41). These DC cultures may be used in a variety of ways, including contacting the DC with antigen to permit uptake, processing and presentation of the antigen (column 6). Applicants note that one of the objectives of *Steinman et al.* was to develop culture methods that do not require the need to enrich for CD34+ progenitor populations (column 46, line 35 and column 50, lines 55-57).

Applicants respectfully submit that the Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 2143.

The presently claimed invention is readily distinguished from the cited art. Neither *Galy et al.* or *Steinman et al.* teach or suggest the use of Flt3-ligand as the primary growth factor in generating dendritic cell populations. *Galy et al.* used a cocktail of 9 cytokines and growth factors to support a broad spectrum of hematopoietic cells. The present claims are not drawn to using a cocktail of cytokines to generate a broad spectrum of hematopoietic cells, but rather, are drawn to using Flt3-ligand to generate dendritic cells. *Steinman et al.* teaches the use of GM-CSF in methods of producing proliferating cultures of DC precursors and mature DC. In short, *Steinman et al.* has absolutely nothing to do with Flt3-ligand. The combination of using a cocktail of 9 cytokines to support a broad spectrum of hematopoietic cells and using GM-CSF in methods of producing proliferating cultures of DC does not teach, suggest or provide the requisite motivation to make the claimed invention.

Secondly, there is not a reasonable expectation of success of developing the claimed method by the teachings of *Galy et al.* and *Steinman et al. Galy et al.* used Flt3-ligand in a cocktail of 9 cytokines and growth factors to generate a heterogeneous population of hematopoietic cells, whereas the clamed method uses Flt3-ligand to develop a dendritic cell population. Clearly, *Galy et al.* teaches away from the claimed invention. Taking the teachings of *Galy et al.* in combination with *Steinman et al.* further teaches away from the claimed invention. The combination of *Galy et al.* and *Steinman*

et al. would result in a method comprising exposing progenitor cells to IL-1, IL-3, IL-6, IL-7, KL, GM-CSF, TNF, Flt3-L and EPO to generate a broad spectrum of hematopoietic cells in combination with adding one or more of GM-CSF, G-CSF, M-CSF, TNF-α, IL-3, IL-1α, IL-1β, IL-6, IL-4, IL-13 and stem cell factor to generate dendritic cells. Again, both references teach away from using Flt3-ligand as the growth factor in generating dendritic cell populations.

Thirdly, the combined prior art references do not teach or suggest all the claim limitations. The limitation of contacting hematopoietic stem and progenitor cells with Flt3-ligand to generate dendritic cell populations is not taught or suggested by *Galy et al.* and/or *Steinman et al.* Applicants note that "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The Examiner states that "one of ordinary skill in the art at the time the invention was made would have been motivated to expose CD34+ progenitor and stem cell populations into dendritic cells incubated with cytokines including Flt3-ligand and GM-CSF with antigen to process and express antigen for various immunological procedures and interventions, known and practiced with dendritic cells at the time the invention was made."

Applicants note that the PTO has failed to cite a reference that provides the requisite motivation to make the claimed invention. Applicants respectfully submit that a conclusion of *prima facie* obviousness must be supported by *evidence*, a showing by some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the claimed invention. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993).

As such, the combination of *Galy et al.* and *Steinman et al.* does not meet the legal standard of *prima facie* obviousness and the rejection under 35 U.S.C. §103(a) should be properly removed.

9. §103(a)

Claims 15, 16, 23-25, 29-32 and 36 stand rejected under 35 U.S.C. §103(a) as being anticipated by *Steinman et al.* (USPN 5,994,126) in view of *Lyman et al.* (USPN 5,554,512) in view of *Inaba et al.* (PNAS 90: 3038-3042, 1993).

Applicants respectfully traverse and submit that the disclosure of *Steinman et al.* in view of *Lyman et al.* in view of *Inaba et al.* does render the present claims obvious under 35 U.S.C. §103(a) and that the combination of references does not meet the legal standard of *prima facie* obviousness.

The disclosure of *Steinman et al.* and the relationship to the present claims has been sufficiently discussed in the section above.

Lyman et al. discloses Flt3-ligand polynucleotide and polypeptide sequences and methods of using Flt3-ligand to expand hematopoietic stem and progenitor cells in a variety of *in vivo* and *in vitro* settings. In these methods, Flt3-ligand may be used alone or in combination with several other cytokines and growth factors. As noted by the Examiner, *Lyman et al.* does not disclose that Flt3-ligand may be used to generate dendritic cell populations.

Inaba et al. teaches that granulocytes, macrophages and dendritic cells arise from a common MHC-II negative progenitor under the influence of GM-CSF.

The Examiner states that "[g]iven that dendritic cells have a common stem cell with other hematopoietic progenitors/stem cells and the cytokines such as GM-CSF provided stimulatory activity to such stem/dendritic cells; the provision of Flt3-ligand and GM-CSF would have been expected to provide stimulatory activity of various hematopoietic cells, including dendritic cells at the time the invention was made." The Examiner reiterates that one of skill in the art would be motivated to make the claimed invention using methods known and practiced with dendritic cells at the time the invention was made.

Applicants respectfully submit that the Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the PTO must show some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.

As to the first element, none of the cited references provide a suggestion or motivation to modify or combine the references to make the claimed invention. *Steinman et al.*, *Lyman et al.* and *Inaba et al.* make no reference whatsoever regarding the use of Flt3-ligand in generating dendritic cell populations. The Examiner relies upon "the

knowledge generally available to one of ordinary skill in the art" as the source for the motivation to combine the references. This point is discussed in detail below.

More importantly, there would not have been a reasonable expectation of success of generating dendritic cells *at the time the invention was made.* This is because all that was known about Flt3-ligand at that time the invention was made (as disclosed in *Lyman et al.*) was that Flt3-ligand was able to stimulate the proliferation of hematopoietic progenitor/stem cells. It was not until *after* Applicants discovered that Flt3-ligand can potently stimulate the generation of downstream cells such as dendritic cells from progenitor/stem cells would one of skill in the art have a reasonable expectation of success. At best, the combined references merely teach or suggest using Flt3-ligand to stimulate the proliferation of hematopoietic stem and progenitor cells and then generating dendritic cells by exposing these cells to GM-CSF. Clearly, this is not the invention being claimed.

Lastly, the combined prior art references do not teach or suggest all the claim limitations. The limitation of contacting hematopoietic stem and progenitor cells with Flt3 ligand to generate dendritic cell populations from hematopoietic stem or progenitor cells is not taught or suggested by *Steinman et al.* and/or *Lyman et al.* and/or *Inaba et al.*

Applicants respectfully submit that the only suggestion for the Examiner's combination of the isolated teachings of the applied references improperly stems from Applicants' disclosure. It goes without saying that it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

As mentioned above, the Examiner's basis for the motivation to combine the references amounts to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because he had the necessary skills to carry out the requisite process steps. As the Examiner knows, this is not the appropriate standard for obviousness. See *Orthokinetics Inc. v. Safety travel Chairs Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986). A high level of skill in the art alone cannot be relied upon to provide motivation to combine prior art references in a manner that would render the claimed invention obvious. *In re Rouffet*, 47 USPQ2d 1453 (CAFC Jul. 15, 1998). The fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. *Ex parte Levengood,* 28 USPQ2d 1300 (BPAI. 1993); MPEP 2143.01.

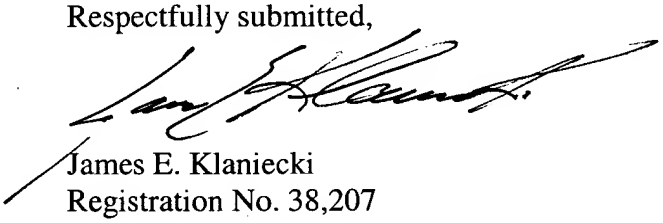
For all these reasons, Applicants respectfully submit that *Steinman et al.* and/or *Lyman et al.* and/or *Inaba et al.* do not render the present claims obvious and do not

satisfy the legal standard of *prima facie* obviousness. As a result, the rejection under 35 U.S.C. §103(a) may be properly withdrawn.

As a final note, claims 15 and 29 are independent claims to methods of preparing dendritic cell populations using Flt3-ligand, which have been shown in the discussion above to be nonobvious over the cited art. Dependent claims 16, 25, 31 and 32 add the step of contacting the dendritic cells with GM-SCF. Applicants note that "if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants respectfully request reconsideration of the pending claims in light of the amendments and arguments presented above. If the Examiner believes that any issues could be resolved, or if the prosecution of the application could be expedited, by a telephone conference, Applicants invite the Examiner to telephone the undersigned at telephone number (206) 265-4145.

Respectfully submitted,



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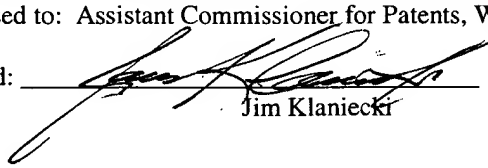
Date: Dec. 18, 2002 Signed: 

Jim Klaniecki

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: David H. Lynch, et al.

Docket No.: 2836-E

Group Art Unit: 1644

Serial No: 09/699,923

Examiner: P. Gambel

Filed: October 30, 2000

For: METHOD FOR PREPARING DENDRITIC CELLS

Version With Markings to Show Changes Made

In the specification:

The "Related Applications" section has been amended as follows:

This application is a divisional of ~~S/N~~ United States Patent Application Serial No. 09/154,903, filed September 17, 1998, ~~pending~~ now abandoned, which is a continuation-in-part of United States Patent Application Serial No. ~~S/N~~ 08/725,540, filed October 3, 1996, now abandoned~~pending~~, which is continuation-in-part of United States Patent Application Serial No. ~~S/N~~ 08/539,142, filed October 4, 1995, now abandoned~~pending~~.

In the claims:

The claims have been amended as follows:

16. The method according to claim 15 further comprising contacting the hematopoietic stem or progenitor cells with ~~a molecule selected from the group consisting of~~ GM-CSF~~, IL-4, TNF α, IL-3, c-kit ligand, fusions of GM-CSF and IL-3, CD40 ligand, and CD40 antibody~~.

23. The method according to claim 15 wherein the flt3-ligand is ~~a recombinant~~ human flt3-ligand.

24. The method according to claim 16 wherein the flt3-ligand is ~~a recombinant~~ human flt3-ligand.

25. The method according to claim 16 wherein the GM-CSF~~molecule~~ is ~~a recombinant~~ human GM-CSF.

31. The method of claim 29, further comprising contacting the dendritic cells with ~~a molecule selected from the group consisting of~~ GM-CSF~~, IL-4, TNF α, IL-3, c-kit ligand, fusions of GM-CSF and IL-3, CD40 ligand, and CD40 antibody~~.

32. The method of claim 31, wherein the GM-CSF~~molecule~~ is human GM-CSF.

36. The method according to claim 29 wherein the flt3-ligand is ~~a recombinant~~ human flt3-ligand.